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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/622,419	08/16/2000	Hartwig Schroder	48792	3392

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KEIL & WEINKAUF
1350 CONNECTICUT AVENUE, N.W.
WASHINGTON, DC 20036

EXAMINER
SAIDHA, TEKCHAND

ART UNIT	PAPER NUMBER
1652	7

DATE MAILED: 05/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/622419	Schroder et al
Examiner	**Group Art Unit**
T. Scaidha	1652

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—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 3/13/03 (Election).

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-14 is/are pending in the application.

Of the above claim(s) II-VII (Claims) are withdrawn is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-6 & 12 (SEQ ID NOS: 1 & 3) is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claim(s) 1-14 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

DETAILED ACTION

1. The Preliminary Amendment and request for reconsideration of the restriction requirement, filed 3.13.03 (Paper No. 6) is acknowledged.

2. ***Election***

Lack of Unity of Invention.

Applicant's election with traverse of Group I, claims 1-6 and 14 in Paper No. 6 is acknowledged. The traversal is on the ground(s) that each of the defined groups other than group VII, contain reference to a combination of S-adenosylmethionine synthase (SAM-synthase) and one of the three identified biotin synthesis genes (bioS1, bioS2 and bioS3). Co-expression of the SAM-synthase gene with one or more of the biotin synthesis genes is a technical feature defining a contribution which each invention, considered as a whole, makes over the prior art.

Applicant's argument is considered and found not persuasive because each combination of SAM-synthase and a biotin synthesis gene as defined by the claim is considered independent and distinct and do not share the same technical feature among the groups. For example the coexpression of SAM-synthase and **bioS1** for biotin production is distinct from the coexpression of SAM-synthase and **bioS2** or coexpression of SAM-synthase and **bioS3**, because in each of these combinations, the structures or activities induced due to presence of bioS1, bioS2 and bioS3 in the gene construct are distinct from one another and therefore not shared among the various groups.

The lack of unity determination is still deemed proper under the PCT treaty and is therefore made FINAL.

3. Claims 1-6 & 12 (in-part) drawn to a process of producing biotin using a host organism transformed with the gene sequence of SEQ ID NO : 1 [SAM-synthase] and the biotin synthesis gene of SEQ ID NO : 3 [bioS1] are under consideration in this examination.

4. Claims corresponding to non-elected groups II-VII are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 6.

5. Priority

Acknowledgment is made of applicants' claim for priority based on an application filed in Germany on 2.19.98.

6. ***Drawings***

Applicants drawing submitted in this application has been approved by the Draftsman.

7. Claims corresponding to groups II-VII are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 6.

8. ***Specification***

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

9. Claim 12 provides for the use of sequences of claim 1 for biotin, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 12 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd. v. Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

10. ***Enablement Rejection***

Claims 1-6 & 12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a process for producing biotin which comprises expressing a S-adenosylmethionine synthase gene of SEQ ID NO: 1 and a biotin biosynthesis gene of SEQ ID NO : 3 in a prokaryotic or eukaryotic host organism able to synthesize dethiobiotin, does not reasonably provide enablement for using any of the functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3 (claims 1, 3-6 & 12), or wherein the deduced amino acid sequences of the gene sequences of SEQ ID NO : 1 & 3 have a homology of 30-100% and enable increased biotin production (claim 2), or express the variously modified sequences in various host organisms irrespective of the host being capable of producing biotin, or its expression in regulation-defective biotin mutants (claims 3-6), either alone or in shared vector or on separate vectors. The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Applicants have described a single construct of co-expression of the combination of metk (SEQ ID NO : 1) and bioS1 (SEQ ID NO : 3) from *Escherichia coli* (see pages 15 of the instant specification). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims are so broad as to encompass a process of using a modified gene of SEQ ID Nos. 1 & 3 for biotin production, wherein the sequences are modified by any extent and includes deletion, substitution or insertion (functional variants); prokaryotic or eukaryotic homologues from bacteria, fungi, plant, animal or human (functional analogues)and truncated sequences thereof; or derivatives (claims 1, 3-6 & 12), or wherein the sequences are modified to having sequence homologies of 30-100% (claim 2) (*see* Specification, page 5, lines 22-47 for Applicants definitions). Applicants have neither disclosed nor described, or exemplified the numerous proposed modifications encompassed by the claims.

The scope of the claims does not commensurate with the enablement provided by the disclosure with regard to the extremely large number of SAM-synthase and/or biotin biosynthesis genes broadly encompassed by the process claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and

guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide sequences of SEQ ID Nos. 1 & 3 from which amino acid sequences can be deduced.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of SEQ ID Nos. 1 & 3 or that ranging in homology from 30-100% identity to the encoded amino acid sequences, because the specification does **not** establish: (A) regions of the protein structure which may be modified without effecting enzyme activity; (B) the general tolerance of enzyme to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any enzyme residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including method or process of using said enzyme(s) with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of process of using such enzymes (SAM-synthase & biotin biosynthesis enzyme) having the desired biological characteristics or its co-expression into any host which may include a host cell not capable of biotin production, is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue in using the modified enzyme in the method claimed. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

11. ***35 U.S.C. § 112, first paragraph (Written Description)***

Claims 1-6 & 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-6 & 12 recite 'functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3. However, description to any such functional variants, analogues or derivatives of SEQ ID Nos. 1 & 3 is lacking (claims 1-6 & 12).

Further claim 2, recite '30-100% homology to the deduced amino acid sequences of SEQ ID Nos. 1 & 3 The specification, however, only provides a process for using a single representative

species of a combination of full length gene sequences from *E. coli* of SEQ ID Nos. 1 & 3 for biotin production. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species to other species where such sequences are conserved in order to establish a relationship among species or modify the enzyme by substitution, insertion or deletion (analogues, variants or derivatives) or make a polypeptide 30-99 % identical to the encoded amino acid sequences deduced from the gene sequences SEQ ID Nos. 1 & 3 and have desired biological activities for biotin production. The specification also fails to describe additional representative species of these combinations by way if modifications such as that claimed by any identifying structural characteristics other than the properties or activity recited in claims, for which no predictability of structure is apparent. Further, description of expressing SEQ ID Nos. 1 & 3 into any prokaryotic or eukaryotic host organism either alone, or on shared vector or on separate vectors is also lacking. Given this lack of additional representative species, such as the proposed modifications of SEQ ID Nos. 1 & 3 and still retain functional characteristics of a process of producing biotin, or various host cells or the expression into single or shared vector, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

12. ***Claim Rejections - 35 U.S.C. § 112*** (second paragraph)

Claim 2 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2, lines 1-4, recite 'claim 1' twice which is not required. Further claim 2, line 3-4, recite 'on the amino acid level deduced from the sequences ...'. The claim is confusing because it is not clearly stated or worded the relationship between the homology and the sequences. Rephrasing the claim to clarify the claim will overcome this rejection.

13. ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3-4 & 12 are rejected under the judicially created doctrine of double patenting over claims 1-7 of U. S. Patent No. 6,436,681 (Schroder et al.) since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows:

Claims are drawn to a process of producing biotin using SEQ ID Nos. 1 & 3 which have been modified to any extent by insertion, deletion or substitution [see Applicants' definition for functional

variants or analogs or derivatives, on page 5]. Such unlimited modifications to the sequences would result in sequences that will read on the process of producing biotin using SEQ ID Nos. 1 & 3 of the patent.

14. ***Allowable Subject matter*** (an example)

Claim 1 : A process for producing biotin which comprises expressing a S-adenosylmethionine synthase gene of SEQ ID NO: 1 and a biotin biosynthesis gene of SEQ ID NO : 3 in a prokaryotic or eukaryotic host organism able to synthesize dethiobiotin, culturing the host organism, separating off the biomass followed by purification and recovery of the biotin.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (703) 305-6595. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (703) 308-3804. The fax phone number for this Group in the Technology Center is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC Saidha

Tekchand Saidha
Primary Examiner, Art Unit 1652
May 12, 2003